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Mode of vagus nerve stimulation differentially affects sleep related breathing in patients with epilepsy

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ABSTRACT

Purpose: We describe the influence of vagus nerve stimulation (VNS) with standard mode and rapid cycling mode on sleep related breathing in two patients with epilepsy.
Methods: Two VNS treated patients underwent digital video-polysomnography for three nights (night 1: rapid cycling mode; night 2: standard mode; night 3: off mode).
Results: In patient 1, on off mode, apnea-hypopnea index (AHI) was 11.1/h, respiratory effort-related arousal index (RERAI) 0.9/h, flow limitation index (FLI) 0.9/h and oxygen desaturation index (ODI) 10.2/h. On standard mode, AHI was 5.5/h, RERAI 1.7/h, FLI 4.1/h and ODI 5.5/h. On rapid cycling mode, AHI was 10.4/h, RERAI 7.9/h, FLI 17.3/h and ODI 10.3/h. In patient 2, on off mode, AHI was 1.6/h, RERAI 0.8/h, FLI 2.2/h and ODI 0/h. On standard mode, AHI was 2.9/h, RERAI 2.4/h, FLI 2.6/h and ODI 2.9/h. On rapid cycling mode, AHI was 0.7/h, RERAI increased to 15.4/h, FLI to 52.0/h and ODI was 0.7/h.
Conclusions: The number of RERAs as well as the number of flow limitations were higher with the rapid cycling mode compared to standard mode and stimulation off and might be related to the higher impulse frequency.

1. Introduction

Vagus nerve stimulation (VNS) is an effective adjunct treatment for medically refractory epilepsy.[1,2] It is hypothesized, that the synchronous electrical stimuli interrupt seizures via the vagus nerve projections in the nucleus tractus solitarius to the brainstem formations, including parabrachial nucleus and locus coerulus.[1]

Several studies have been published analyzing the effect of stimulation parameters on seizure frequency in refractory epilepsy.[3,4] Several stimulation modes have been applied (standard: stimulation for 30 s followed by a stimulation-free period of 5 min, pulse width of 500 μs) and a significantly higher efficacy of VNS with the rapid cycling mode (cycles of 7-s stimulation with a stimulation-free interval of 12 s) have been described).[3,4] Efficacy appears to increase over time. In general, one third of the patients show a >50% reduction of seizure frequency; one third show a 30–50% seizure reduction, and one third of patients show no response. Few patients become seizure-free. Side effects during stimulation are mainly voice alteration, coughing, throat paraesthesia and discomfort.[2] Frequent side effects of long-term VNS treatment include cough, voice alteration, dyspnea and paresthesia.[5]

Moreover, during sleep, an increased apnea-hypopnea index (AHI) was shown.[5,6] Besides, two case studies have reported VNS related tachypnea and apnea.[7,8]

Analysis of different settings (standard mode versus rapid cycling mode) of VNS on sleep related breathing, however, has not been performed.

We investigated the influence of different settings of VNS (standard mode versus rapid cycling mode versus stimulation off) on sleep related breathing in two patients with focal epilepsy.

2. Methods

2.1. Patients

Two male patients with medically refractory focal epilepsy who had undergone VNS device implantation previously participated in this study. The vagus nerve stimulation (VNS) device (Neurocybernetic Prosthesis System; Cyberonics Inc., Houston, Texas, USA) was implanted according to standard methodology.[5] Patient 1 was a 35-year-old man diagnosed as cryptogenic epilepsy with simple partial (SP), complex partial (CP) and generalized tonic clonic seizures (TC). At the time of polysomnography (PSG) he was treated with levetiracetam 3000 mg, phenobarbitone 400 mg and carbamazepine 1650 mg per day. Patient 2 was a 36-year-old man with symptomatic epilepsy after fronto-temporal osteoplastic craniotomy for craniopharyngioma in 1978. He had SP, CP and

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generalized TC seizures. At the time of PSG he was on levetiracetam 3000 mg and phenytoin 600 mg per day.

At admission to the hospital, both patients were on standard mode VNS setting consisted of on/off cycles of 30 s every 5 min, with each on cycle consisting of 500-μs duration pulses at 30 Hz; output current was increased as tolerated to a intensity of 0.75 mA.

2.2. Polysomnography

Polysomnographies were performed at the Sleep Disorders Unit, Department of Neurology, Innsbruck Medical University. Digital polysomnography (Schwarzer Brainlab for Windows Version 4.00; Munich, Germany) included electroencephalography (EEG) (C3-A2, C4-A1, O1-A2, O2-A1), horizontal and vertical electrooculogram (EOG), bipolar surface electromyography of mental, submental, and both tibialis anterior muscles. Cardiorespiratory monitoring consisted of nasal and oral airflow (thermocouple, nasal pressure cannula), tracheal microphone, thoracic and abdominal respiratory effort (Piezo), finger oximetry and one lead electrocardiogram. Infrared video was recorded during the whole night and digitally stored.

Since the new standard criteria of the American Academy of Sleep Medicine (AASM)[9] were not published at time of investigation, sleep was recorded and visually scored in 30 s epochs according to Rechtschaffen and Kales. The scoring of respiratory events was retrospectively performed according to AASM 2007 standard criteria[9] with the limitation that we used piezoelectric registration instead of plethysmography for measuring thoracic and abdominal respiratory effort. An obstructive apnea was defined as a 90% decrease in airflow from baseline amplitude for ≥10 s. A hypopnea was defined as a ≥30% decrease in airflow for ≥10 s with a ≥4% oxygen desaturation from pre-event baseline. The AHI for each night is the sum of apneas and hypopneas divided per hour of sleep. Respiratory effort-related arousals (RERAs) were scored as a increase of respiratory effort or flattening of the nasal pressure waveform with a duration of ≥10 s leading to an arousal from sleep. RERA index (RERAI) for each night is the sum of RERAs divided per hour of sleep. Additionally, we scored flow limitations (FL) as a increase of respiratory effort or flattening of the nasal pressure waveform with a duration of ≥10 s which were not associated with an arousal from sleep or an oxygen desaturation. Flow limitation index (FLI) for each night is the sum of flow limitations divided per hour of sleep. The oxygen desaturation index was calculated, as the sum of oxygen drops larger than 4% from the immediately preceding baseline per hour of sleep. Both patients underwent three nights of digital video-polysomnography: the first night on rapid cycling mode and the second night on standard mode. Intensity of output current (0.75 mA) and 500-μs duration pulses at 30 Hz were not changed between one PSG and the other.

Additionally in both patients during hospitalization due to pulse generator change a third PSG night on off-mode was recorded. Both patients were on stable doses of antiepileptic medications.

Table 1
Sleep variables of patients 1 and 2.

VNS parameter	Patient 1			Patient 2		
	Off	SM	RCM	Off	SM	RCM
Time in bed (TIB) (min)	490.5	477.0	481.5	488.0	475.0	481.0
Sleep period time (SPT) (min)	471.5	465.5	463.0	486.5	471.0	473.5
Sleep latency[a] (min)	12.0	11.5	18.5	1.5	4.0	7.5
REM latency (min)	183.0	76.5	71.5	90.0	167.5	101.0
Sleep efficiency[b] (SE) (%)	80.0	71.5	89.5	95.4	97.5	84.8
Wakefulness (min SPT)	79.0	124.5	32.0	21.0	8.0	65.5
Stage 1 (min SPT)	95.0	44.5	81.0	68.0	71.0	50.5
Stage 2 (min SPT)	209.0	156.5	205.5	265.5	314.0	281.0
Stage 3 + 4 (min SPT)	56.5	107.0	107.5	43.5	12.0	40.0
REM (min SPT)	32.0	32.5	33.5	80.5	63.0	35.0
Time in body position (min)[c]						
Supine position	392.5	328.5	333.5	280.5	177.5	334.5
Side position	0	0	71.5	177.0	282.5	72.5

[a] Sleep latency (first epoch of stage 2 or three consecutive epochs of stage 1).
[b] Sleep efficiency: ratio of total sleep time to time in bed expressed in percent.
[c] Prone position was not registered in both patients.

Table 2
Respiratory variables and their association with arousals, body position and sleep stages.

VNS parameter	Patient 1			Patient 2		
	Off	SM	RCM	Off	SM	RCM
Respiratory variables:						
Apnea-hypopnea index (AHI) (Association with arousals, %)	11.1 (88.9)	5.5 (80.6)	10.4 (74.3)	1.6 (66.7)	2.9 (20.0)	0.7 (59.2)
Apnea index (AI)	4.0	0.0	7.1	0.0	0.0	0.0
Hypopnea index (HI)	6.1	5.5	3.3	0.4	2.9	0.7
RERA index (RERAI)	0.9	1.7	7.9	0.8	2.4	15.4
Flow limitation index (FLI)	0.9	4.1	17.3	2.2	2.6	52.0
Oxygen desaturation index (ODI)	10.2	5.5	10.3	0.4	2.9	0.7
Basal oxygen saturation (%)	97.0	92.0	94.0	96.0	96.0	95.0
Mean oxygen saturation (%)	94.3	93.9	94.1	96.4	94.1	96.0
Minimal oxygen saturation (%)	76.0	77.0	74.0	92.0	81.0	88.0
Respiratory variables in association with body position						
Supine position						
AHI	11.1	5.5	13.1	0.6	6.4	0.9
RERAI	0.9	1.7	8.6	1.0	2.0	14.5
Side position						
AHI	0.0	0.0	1.7	0.7	0.8	0.0
RERAI	0.0	0.0	7.6	0.0	2.8	19.9
Respiratory variables in association with sleep stages:						
Non-REM sleep						
AHI	5.7	1.2	7.9	0.3	2.9	0.3
RERAI	0.8	1.9	7.9	0.8	2.9	16.0
REM sleep						
AHI	60.0	48.5	41.2	0.7	3.8	5.1
RERAI	1.9	0.0	0.0	0.7	0.0	10.3

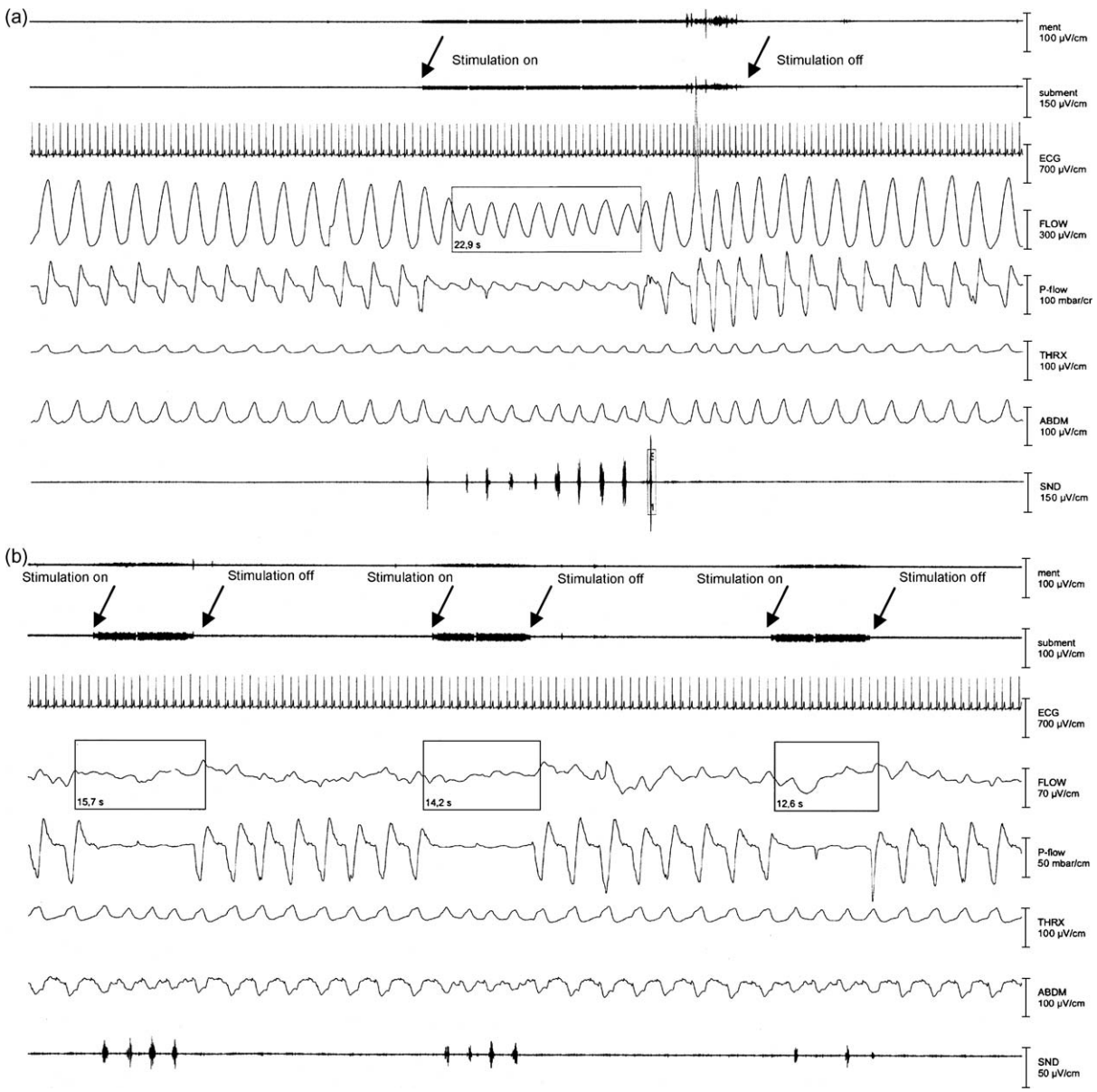

Fig. 1. (a) The 120 s stage 2 sleep epoch out of the PSG night with VNS on standard mode in patient 2 shows one single vagus nerve stimulus as an artifact on the EMG channels of mental and submental muscles (solid arrow) simultaneously with a respiratory event related arousal (RERA). (b) The 120 stage 2 sleep epoche of PSG night with VNS on rapid-cycling-mode in patient 2 shows three vagus nerve stimuli (solid arrows) coinciding with respiratory effort-related arousals (RERAs).

3. Results

Sleep variables of each patient for all three PSG nights with the different VNS settings are given in Table 1. In both patients, the number of RERAs was higher with the rapid cycling mode compared to standard mode and stimulation off. In line with this finding, there was a striking increase of flow limitations with the rapid cycling mode. AHI and ODI were not effected by the different settings of VNS. The RERA indices were not influenced by changes of body position or different sleep stages. The effect of differential settings of vagus nerve stimulation (VNS) on respiratory parameters as well as the association with arousals, body position and sleep stages are shown in Table 2. An example of the close temporal relationship between vagus nerve stimulus and RERAs is shown in Fig. 1a and b. Fig. 1a shows a 120 s epoch recorded in patient 2 with VNS on standard mode during stage 2 sleep. A single vagus nerve stimulus appears as an artifact in the EMG channels of mental and submental muscles coinciding with a RERA. Fig. 1b corresponds to a 120 s stage 2 epoch obtained during the PSG with VNS on rapid cycling mode in the same patient. Compared to the epoch during PSG on standard mode three vagus nerve stimuli with simultaneous RERAs appears in the same time window. On the other hand, at visual inspection, arousals also occurred – independently from respiratory events – in the context of VN stimuli. Both patients had no seizures during overnight recordings.

4. Discussion

This study shows that the mode of VNS (rapid cycling mode versus standard mode versus stimulation off) differentially affects respiration during sleep. We observed a striking increase of the respiratory effort-related arousal index as well as the flow limitation index on rapid cycling mode compared to standard mode or stimulation off. This effect was independent of pre-existing mild sleep-related breathing disorder (patient 1), body position, or sleep stage. We do not know if changing the output

current and pulse width would have additionally influenced sleep related breathing in our patients, since previous studies reported divergent findings concerning the influence on respiration during sleep by these VNS threshold settings. Malow et al. observed that stimulus frequency reduction ameliorated VNS related apneas and hypopneas,[6] whereas there was no change in apneas and hypopneas with stimulus intensities from 0.25 to 0.5 mA and pulse widths of 500 and 125 μs on standard mode.[6] In contrast to these findings, Zaaimi et al. reported a positive correlation between stimulus intensity from 1 to 3 mA and thoracic distension signals.[10] However, intensity of output current (0.75 mA) and 500-μs duration pulses at 30 Hz were not changed between one PSG and the other, but stimulation mode.

A close temporal relationship between RERAs and VNS stimulation were observed (see Fig. 1a and b). We can only speculate that the higher number of RERAs as well as the number of flow limitations with rapid cycling mode compared to standard mode is related to the higher impulse frequency. In rapid cycling mode off to on time is 23–7 s (equivalent to 23.3% of stimulation cycle time), in standard mode off to on time is 270–30 s (equivalent of 10% of stimulation cycle time). In fact, while on rapid cycling mode with more frequent stimulation cycles and higher total time of stimulation on, in both patients a higher RERA index and FL index was observed (see Table 1).

The RERAs might be caused by partial airflow limitation induced by potential central and peripheral effects of VNS.[6] In fact, glottic dyskinesia has been observed during VNS by using fiberoptic laryngoscopy.[11]

There was a high interindividual difference in the increase of RERAs from off mode to rapid cycling mode (approximately 10-fold versus 20-fold increase). Even more striking was the increase of flow limiations, although the clinical relevance is uncertain. One possible explanation may be the different antiepileptic drug regimen. In fact, patient 2 was on phenytoine which was found to impair peripheral chemoreceptor responses to hypoxia in the animal model.[12]

There are several potential limitations of our study. First, it is a preliminary investigation in only two patients. Second, we used piezoelectric registration for measurement of respiratory effort instead of the gold standard plethysmography.[9] Third, we only scored respiratory event related arousals. We did not perform an analysis of VN stimulus related arousals since in polysomnography the stimulus was not always visualized. In summary, these cases suggest that respiration during sleep should be carefully investigated in patients who undergo VNS stimulation especially in rapid cycling mode. In case of a significant increase of RERAs as well as flow limiations specifically if it reaches clinical significance, a change in VN stimulus mode or treatment with nasal CPAP should be considered. Further studies with larger number of patients will be needed to investigate the influence of different VNS modes not only on sleep breathing, but also on arousals in general (cycling alternating pattern) and daytime sleepiness.

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